



Baylor  
College of  
Medicine

# Brain Imaging of Veterans and Service Members with Chronic Mild TBI

Harvey Levin, PhD

Supported by Dept of Veterans Affairs Merit Review and Center of Excellence for Traumatic Brain Injury, and NINDS P01 NS056202

## Acknowledgement: Imaging Core, Neurons to Networks Center of Excellence

- Rajan Agarwal, MD-neuroradiologist
- Shalini Mukhi, MD-neuroradiologist
- Mary Newsome, PhD-fMRI, resting state
- Randall Scheibel, PhD-task-related fMRI
- Brian Taylor, PhD-MR physicist
- Elisabeth Wilde, PhD-structural MRI, DTI
- Xiaodi Li, BA-Image data analyst
- Vanessa Abadia, M Ed-Image data analyst

# Goals of Presentation

- Issues in diagnosing chronic mTBI in Veterans
- Volumetric MRI
- Cortical thinning
- Diffusion tensor imaging (DTI)
- Resting state fMRI- functional connectivity
- Task-related fMRI and dissociation of mTBI vs PTSD effects

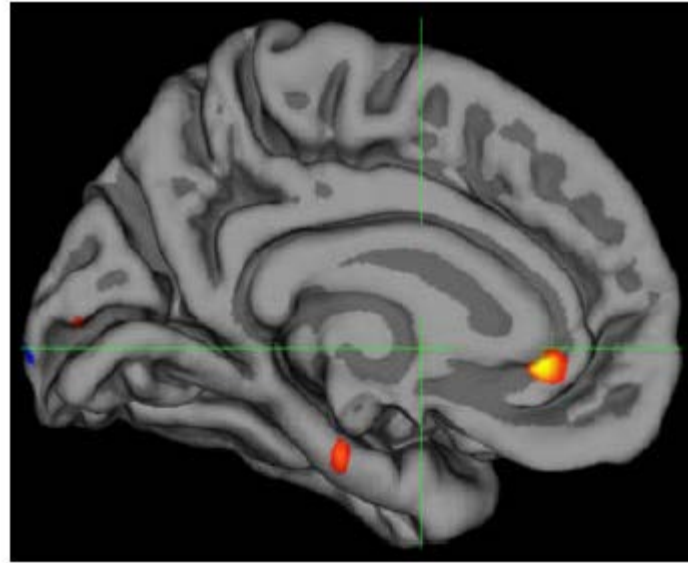
# Challenges in Diagnosing Chronic mTBI in OEF/OIF/OND Veterans

- Diagnosis often relies on self-report without acute medical records; co-morbid PTSD/depression partially overlap in Sx with mTBI. Substance abuse could affect MRI findings.
- Lack of reference data to identify subtle cortical atrophy and reduced brain region volumes on MRI.
- DTI metrics are potentially robust imaging biomarkers for mTBI, but center differences in equipment, software, QA, and method of analysis

# Gray and white matter volumes in Veterans with chronic blast-mTBI (n=30) and controls (n=12)

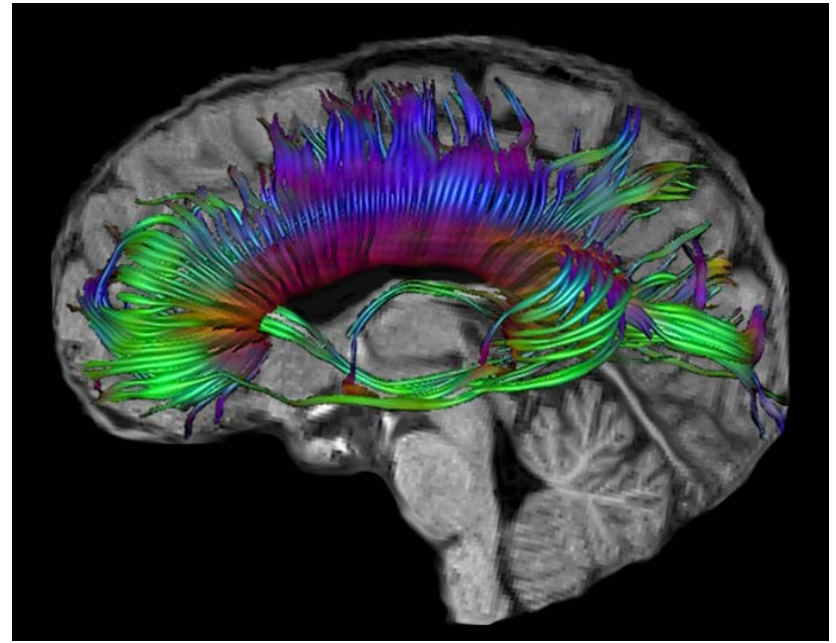
Region	Volume (in mm <sup>3</sup> )		p-value	ES (Cohen's f)
	TBI LSM	OI LSM		
<b>R Cerebral WM</b>	<b>235258.31</b>	<b>245411.22</b>	<b>0.14</b>	<b>0.25</b>
L Cerebral WM	235360.50	244887.76	0.19	0.22
R Cerebral GM	272144.64	270601.98	0.83	0.04
L Cerebral GM	271461.18	270578.21	0.90	0.02
<b>R Cerebellar WM</b>	<b>14380.74</b>	<b>16859.06</b>	<b>0.009</b>	<b>0.44</b>
<b>L Cerebellar WM</b>	<b>15489.08</b>	<b>17472.64</b>	<b>0.06</b>	<b>0.31</b>
R Cerebellar GM	54555.87	555241.84	0.84	0.03
L Cerebellar GM	54023.40	53478.91	0.86	0.03

R: right, L: left. TBI: traumatic brain injury; OI: orthopedic injury; LSM: least squares means; ES: effect size; GM: gray matter; WM: white matter. For Cohen's f, 0.25 is a moderate and 0.40 is a large effect size. Volumes are represented in cubic millimeters.

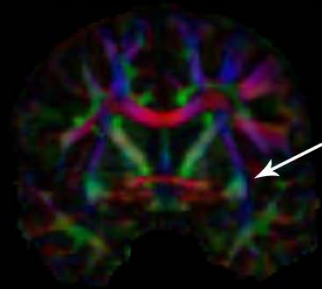


**Cortical thinning in anterior cingulate and parahippocampal gyrus in Veterans imaged 5 years post-blast related mTBI (n=12) as compared with Veterans who had no TBI during deployment (n=8)**

# Diffusion Tensor Imaging



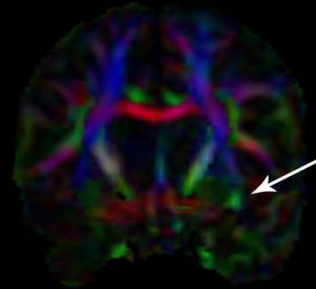
Control



R

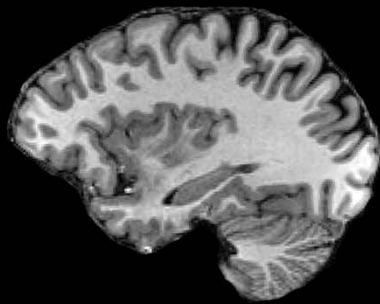
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TBI



R

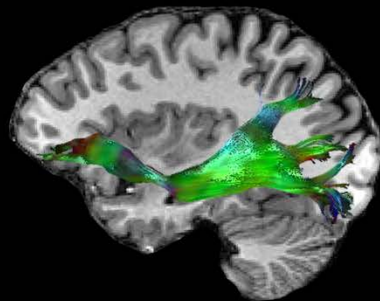
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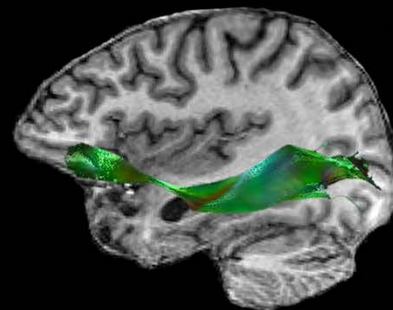
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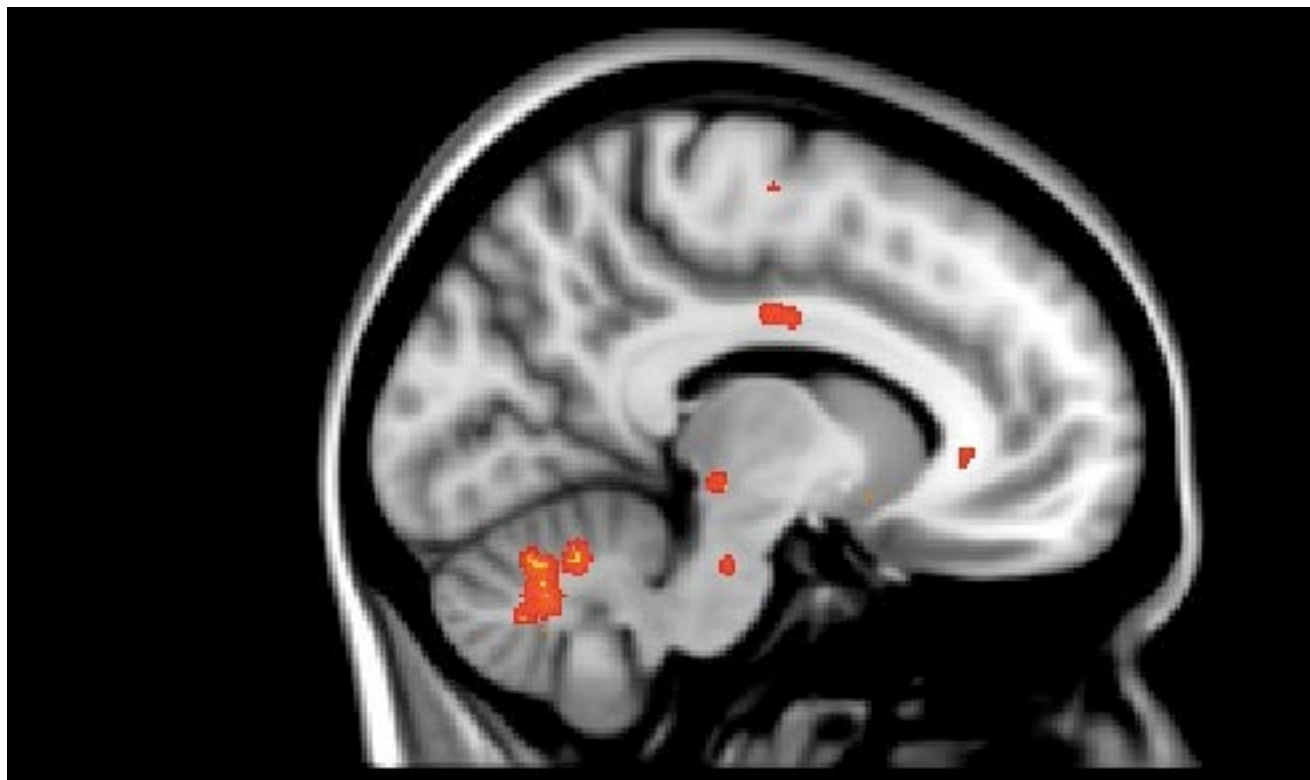


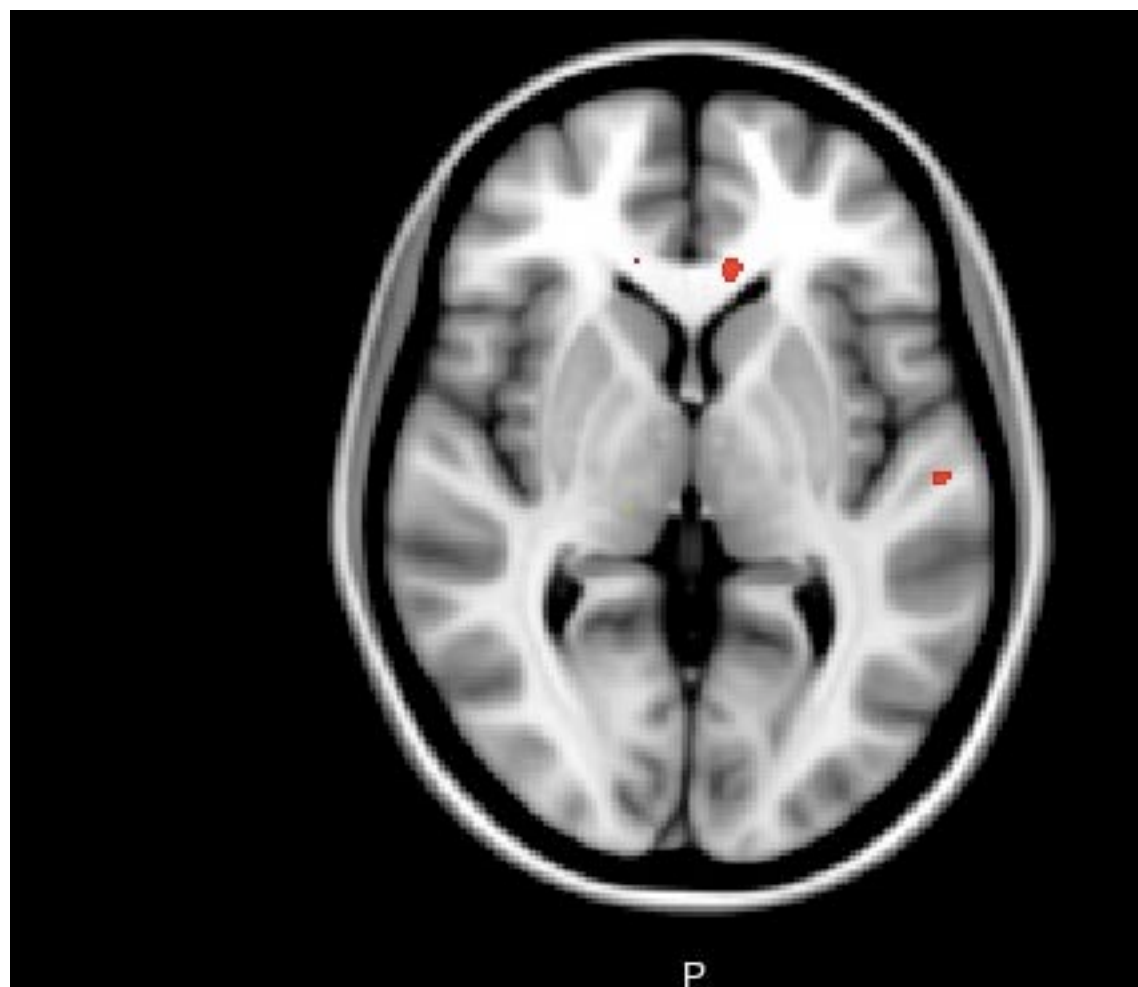
L



# **DTI Data from Ongoing Merit Review Project of Chronic mTBI in Veterans**

- Used tract based spatial statistics (TBSS) to compare mTBI (n=19) with post-deployed group without TBI (n=13) who were not exposed to blast.
- Fractional anisotropy (FA), a metric which reflects preferential diffusion of water parallel to tract, shows areas of reduced integrity of microstructure including corpus callosum, brain stem, and cerebellum.

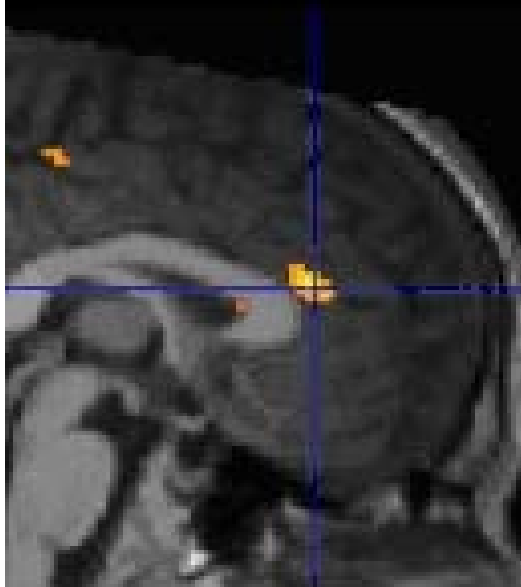




# Preliminary fcMRI Findings

- 17 Veterans were imaged 5 years post-mTBI (mean age = 31.4 yrs, sd = 6.2) as were 15 control Veterans unexposed to blast and without TBI (31.2 yrs, sd=5.9, sd = 2.2)
- Groups did not differ in age or education
- In the scanner, subjects were instructed to close their eyes but not fall asleep.

**Reduced Connectivity**



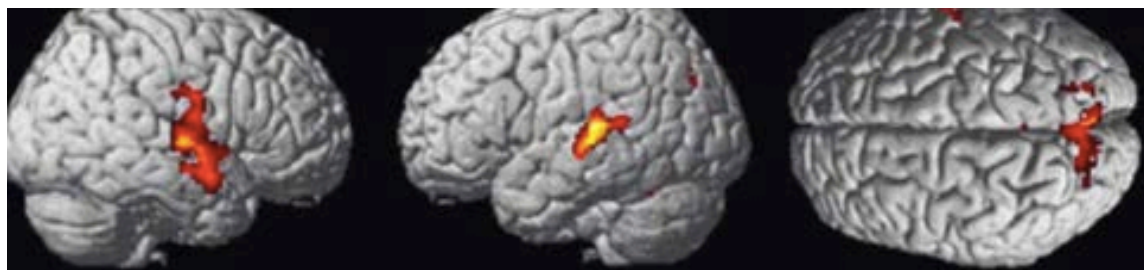
**B. Increased Connectivity**



**Functional connectivity (FC) of PCC and ACC was reduced in Veterans imaged 5 years post-mTBI (n=17) as compared with controls (n=15); PCC connectivity with left prefrontal cortex was greater after mTBI.**

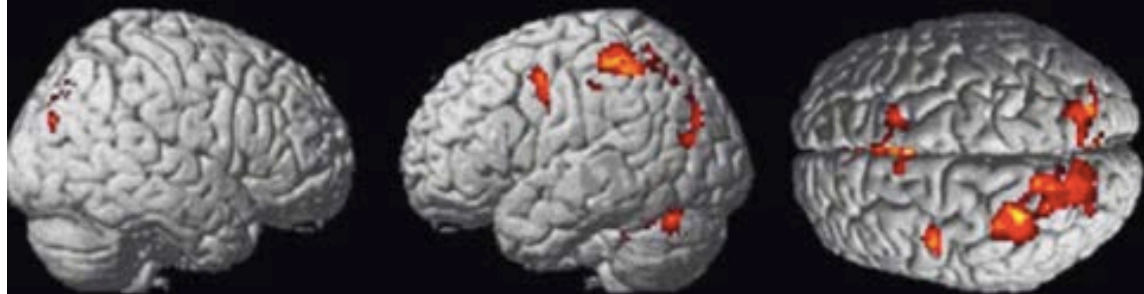
## **Altered brain activation in military personnel after $\geq 1$ TBI from blast. Scheibel et al (JINS 2012, 18:89-100)**

- Compared OEF/OIF groups with TBI (n=15) vs no TBI on stimulus-response compatibility task.
- TBI was co-morbid with high PTSD symptoms
- Pressed button on side pointed to by blue arrows, but opposite of red arrow direction
- TBI group had more activation in mesial prefrontal cortex, anterior cingulate gyrus and posterior regions after statistically controlling for group differences in PTSD, depression and RT .
- PTSD dampened frontal-temporal activation



+

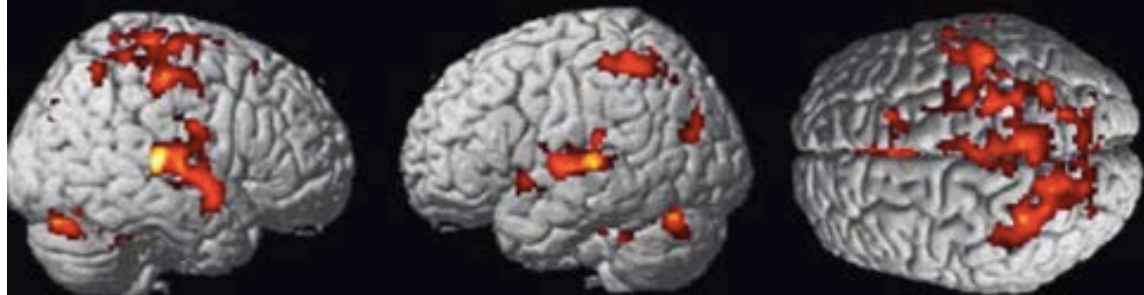
) T-Test TBI > Controls



) ANCOVA TBI > Controls

Covariates: PCL-C, BSI Depression Scale, Red Arrows RT, Blue Arrows RT

Posterior

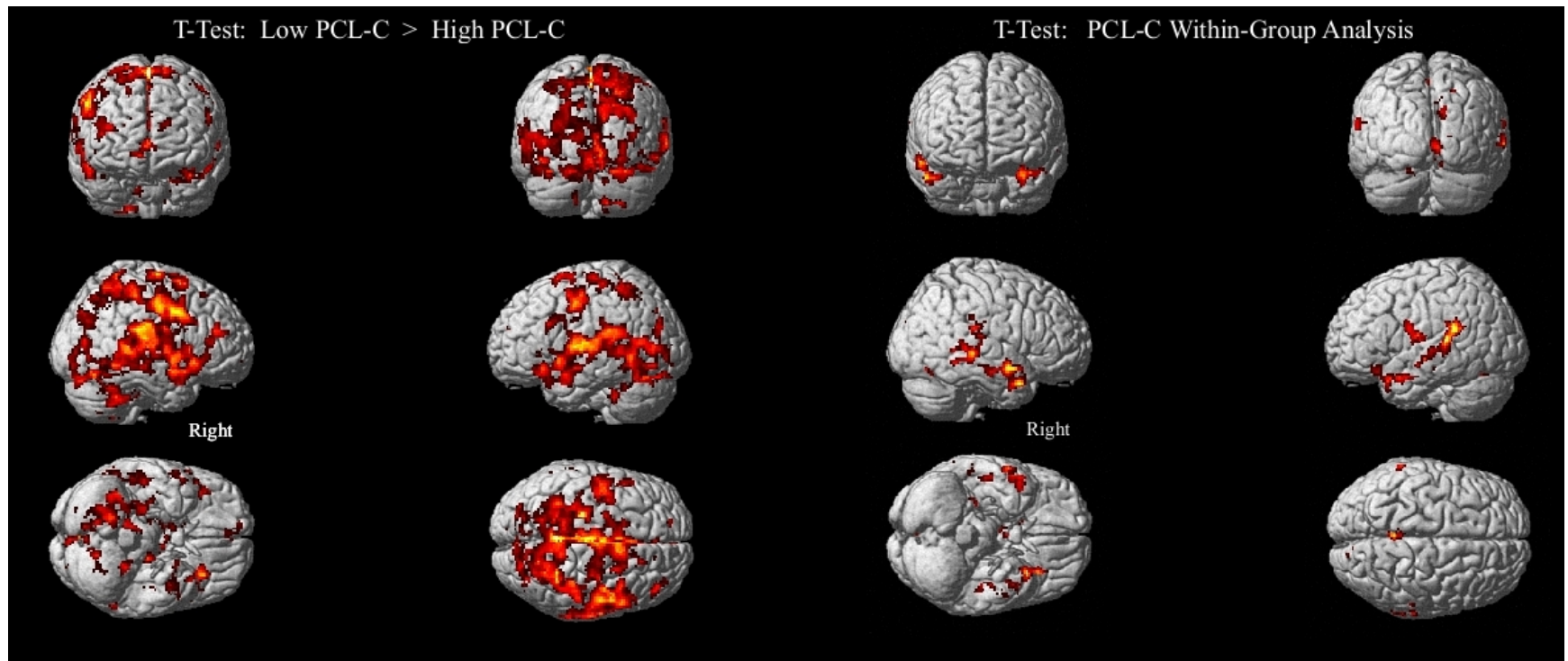


Right Lateral

Left Lateral

Top

Figure 2 Modulation of cognitive control activation by PTSD symptom severity. Images on the left depict areas where veterans with lower scores on the PCL-C had greater Arrows task activation, relative to veterans with higher PCL-C scores. Figures on the right indicate brain areas where veterans with lower PCL-C scores had significant activation during the Arrows task. (Scheibel et al., 2012)





# Summary

- Volumetric MRI, DTI, resting state fMRI and task-related fMRI are sensitive to chronic effects of predominantly mild TBI primarily due to blast
- DTI is sensitive to chronic mTBI.
- Functional connectivity in Veterans with chronic mTBI differs from controls in DMN.
- Co-morbid PTSD reduces activation in task-related fMRI, opposite to effects of chronic mTBI

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# Advanced Imaging and Analytic Methods for Mild TBI

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- **Part I**

Inter-individual spatial heterogeneity of tissue damage  
from concussive injury

- **Part II**

Tissue damage from subconcussive exposure to blast

# Background

- Exposure to explosive forces from bombs is common in Veterans of recent military conflicts
- Majority of traumatic brain injury (TBI) at forward deployed medical facilities involves exposure an improvised explosive device (IED), grenade, rocket-propelled grenade (RPG), or mortar fire.
- Damage to brain tissue (white matter) using Diffusion Tensor Imaging (DTI) is well established in cases that clinical symptoms of mild TBI.
- Recent studies of sports participants show compromised white matter integrity even in the absence of clear concussive symptoms – subconcussive exposure.
- Until very recently, subconcussive exposure was not associated with “injury”

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## RESEARCH LETTER

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### **White Matter Integrity in the Brains of Professional Soccer Players Without a Symptomatic Concussion**

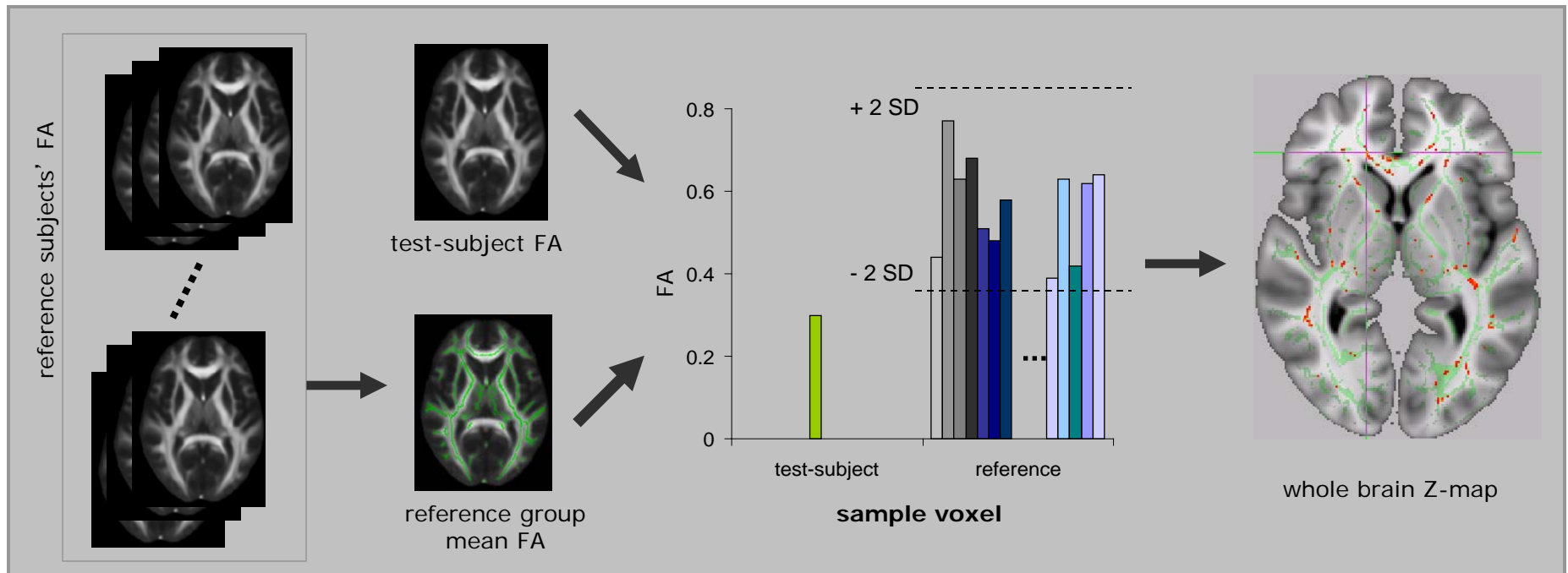
To the Editor: Soccer is the most popular sport in the world, with more than 250 million active players.<sup>1</sup> It is the only sport in which the unprotected head is a primary point of contact when heading the ball. In other contact sports, the deleterious long-term effects of repetitive traumatic brain

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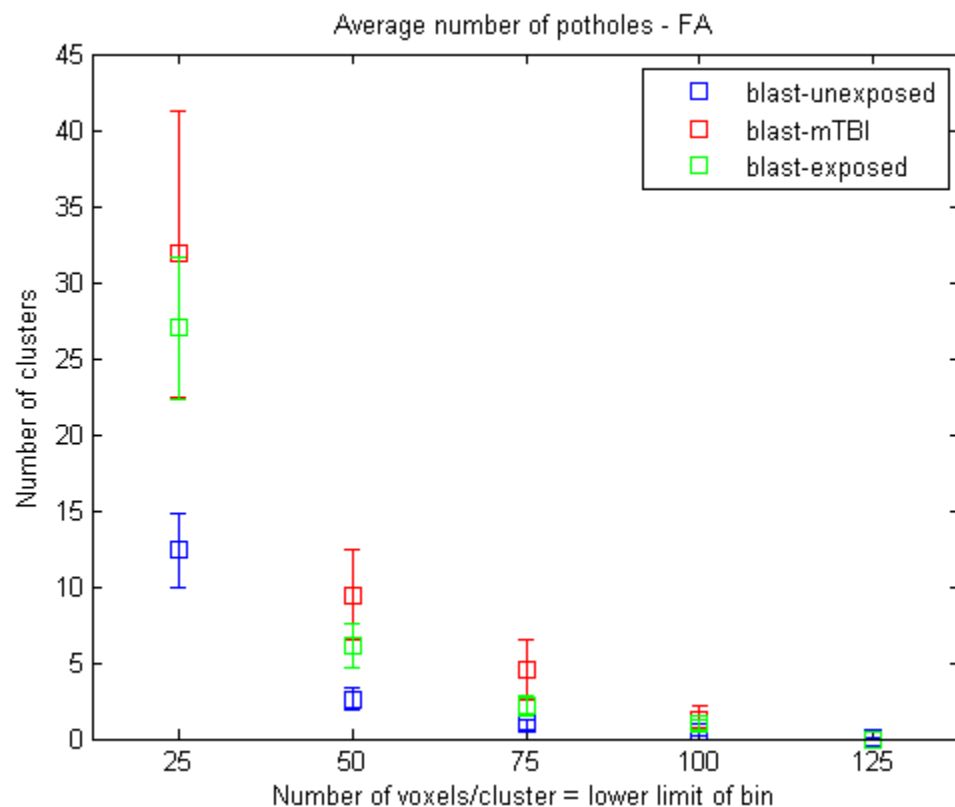
# Question

Is the injury to brain tissue in Veterans with blast exposure without clinical symptoms of TBI ?

- A) YES
- B) NO
- C) NOT SURE



**Figure 1.** Following preprocessing of DTI data, the analytic approach was based on registration of FA maps as implemented in the FSL tract based spatial statistics (TBSS). The primary statistical approach used the standard deviation of fractional anisotropy for each voxel in the reference group. Using the mean and standard deviation of FA for the reference group, the test-subject's voxels were compared to the skeleton voxels (green highlight) that were generated for the reference group. For the test-subject, we computed a statistical map that reflects the number of standard deviations below the mean of the reference group, which is effectively a z- map. The whole brain z-map shows voxels (in red) where FA of the test-subject was found to be greater than two standard deviations below the mean FA of the reference group.

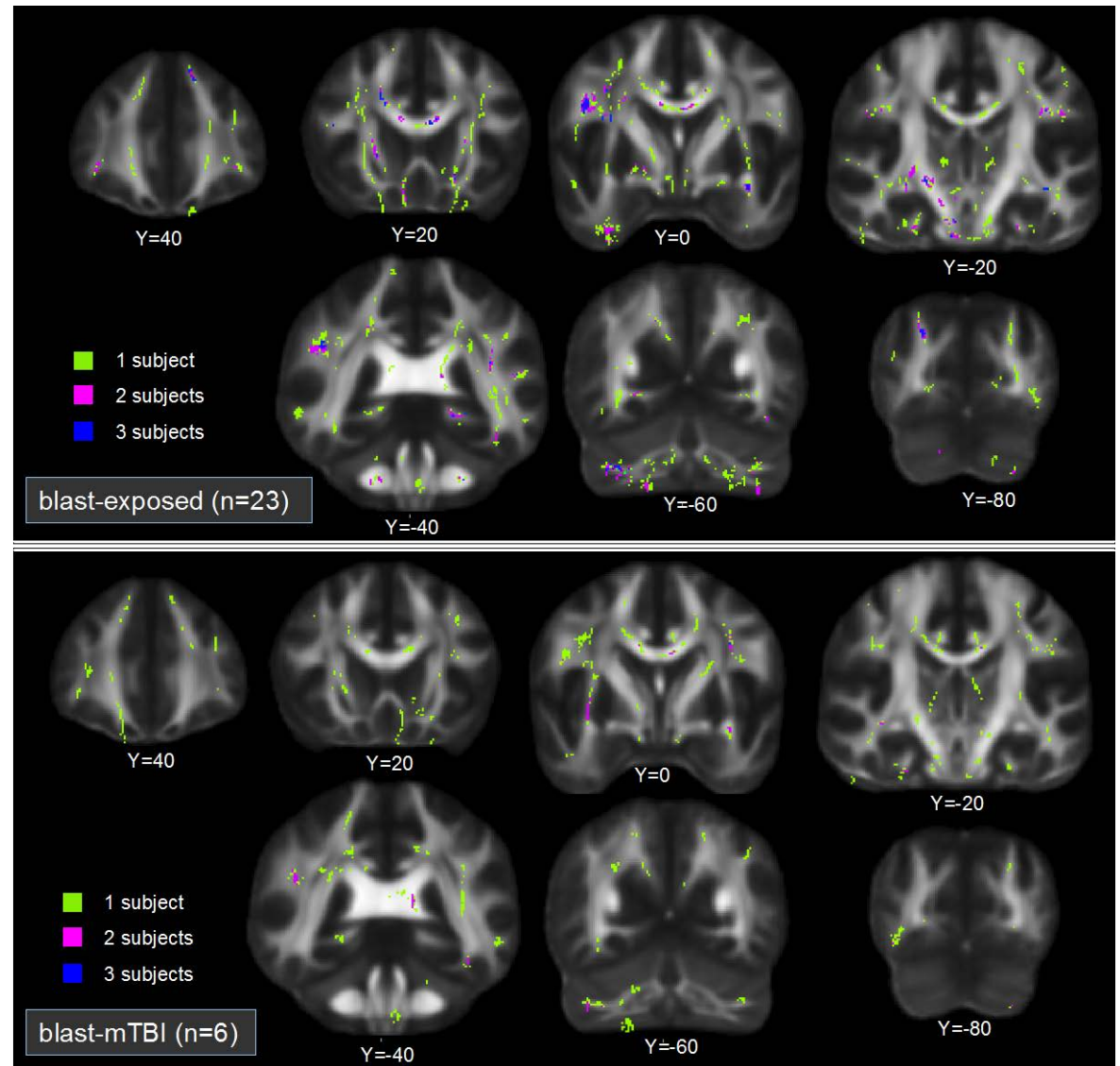


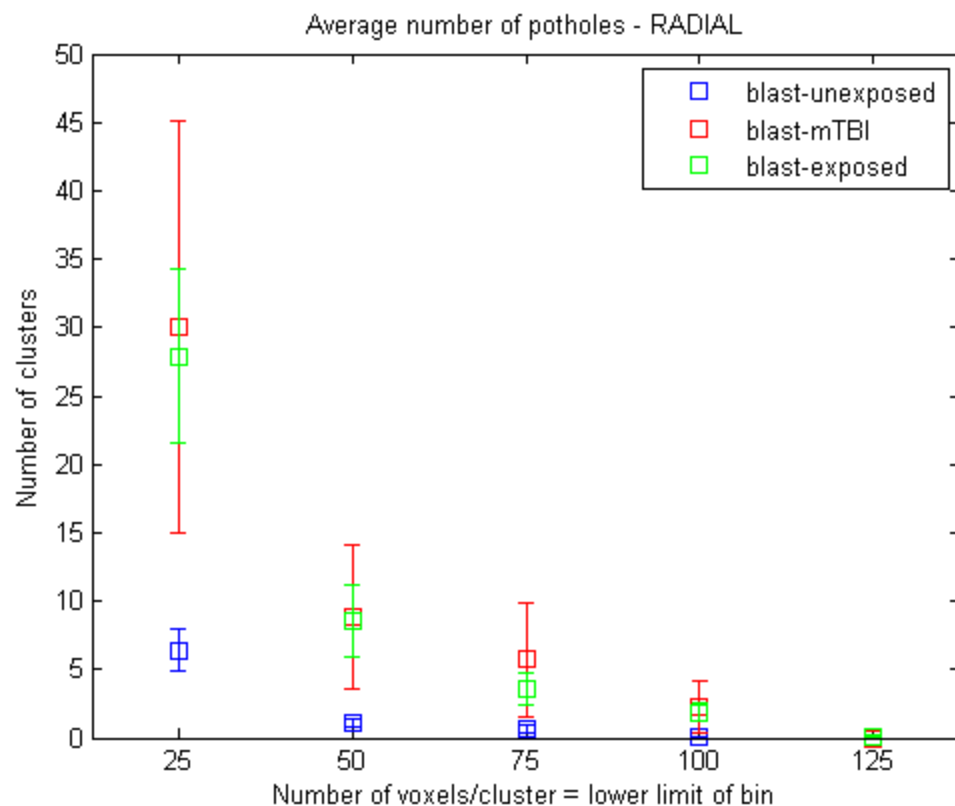
**Figure 2.** There was a significant main effect of group [ $F(2,42)=4.4$ ,  $p=.02$ ] on the number of small (25-50 voxel), medium (50-75 voxel), and large (75-100 voxel) potholes, which were defined by low FA values ( $z < -2$ ). The blast-unexposed control group had significantly fewer potholes than the blast-mTBI group ( $p = .009$ ) and the blast-exposed group ( $p = .036$ ). Based on the number of potholes, the blast-exposed group resembled the blast-mTBI group when considered in relation to the blast-unexposed control group



# Damage is spatially dispersed because of heterogeneous mechanisms of injury

- Damage is spatially dispersed
- Damage is spatially heterogeneous across patients



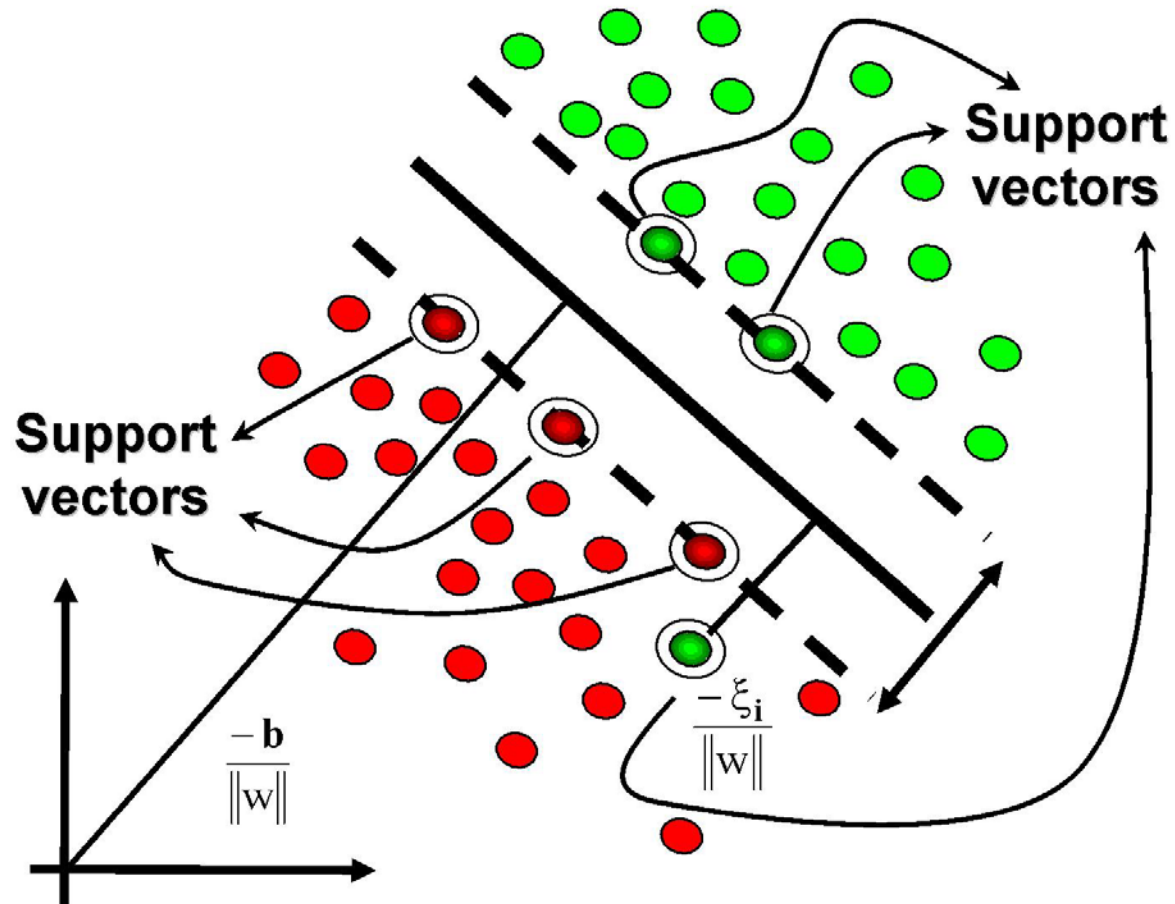


**Figure 4.** There was a significant main effect of group [ $F(2,42)=3.7$ ,  $p=.034$ ] on the number of small (25-50 voxel), medium (50-75 voxel), and large (75-100 voxel) potholes, which were defined by low radial diffusivity ( $z < -2$ ). The blast-unexposed control group had significantly fewer radial diffusivity potholes than the blast-mTBI group ( $p = .032$ ) and the blast-exposed group ( $p = .025$ ). Based on the number of potholes, the blast-exposed group resembled the blast-mTBI group when considered in relation to the blast-unexposed control group.

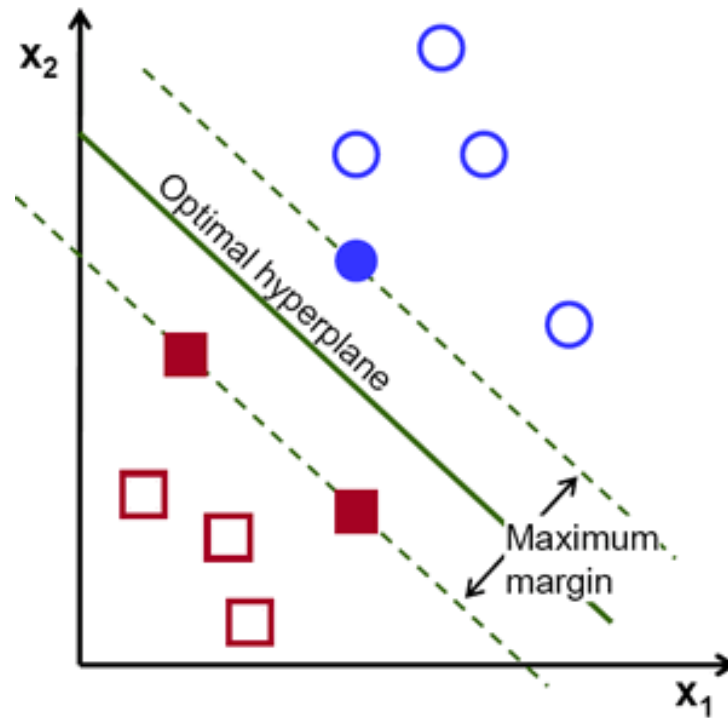
# Association with neuropsychological measures

- We found significant association with intra-extra dimensional shift (IED; Cambridge Cognition).
- Tests learning by inferring rules and set-shifting
- Hierarchical linear regression models including age, race, education, PTSD symptoms, MDD symptoms, and DTI measures
- These significantly predicted the
  - IED-number of stages completed [ $F(7,37)=2.4$ ,  $p<.04$ ]
  - IED-post-shift percent errors [ $F(7,37)=2.8$ ,  $p<.02$ ];
  - Simple reaction time [ $F(7,37)=5.8$ ,  $p<.001$ ];
  - Number of errors on the spatial working memory [ $F(7,37)=2.3$ ,  $p<.05$ ].

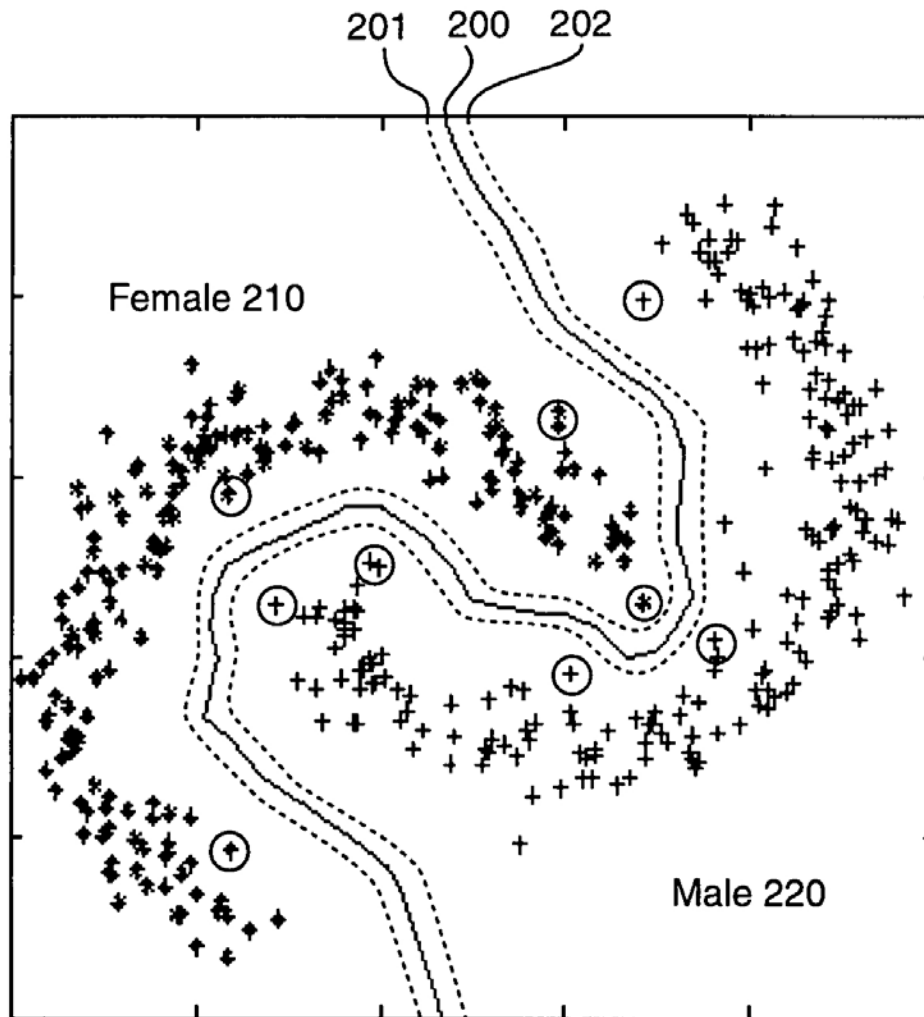
# Support vector machine



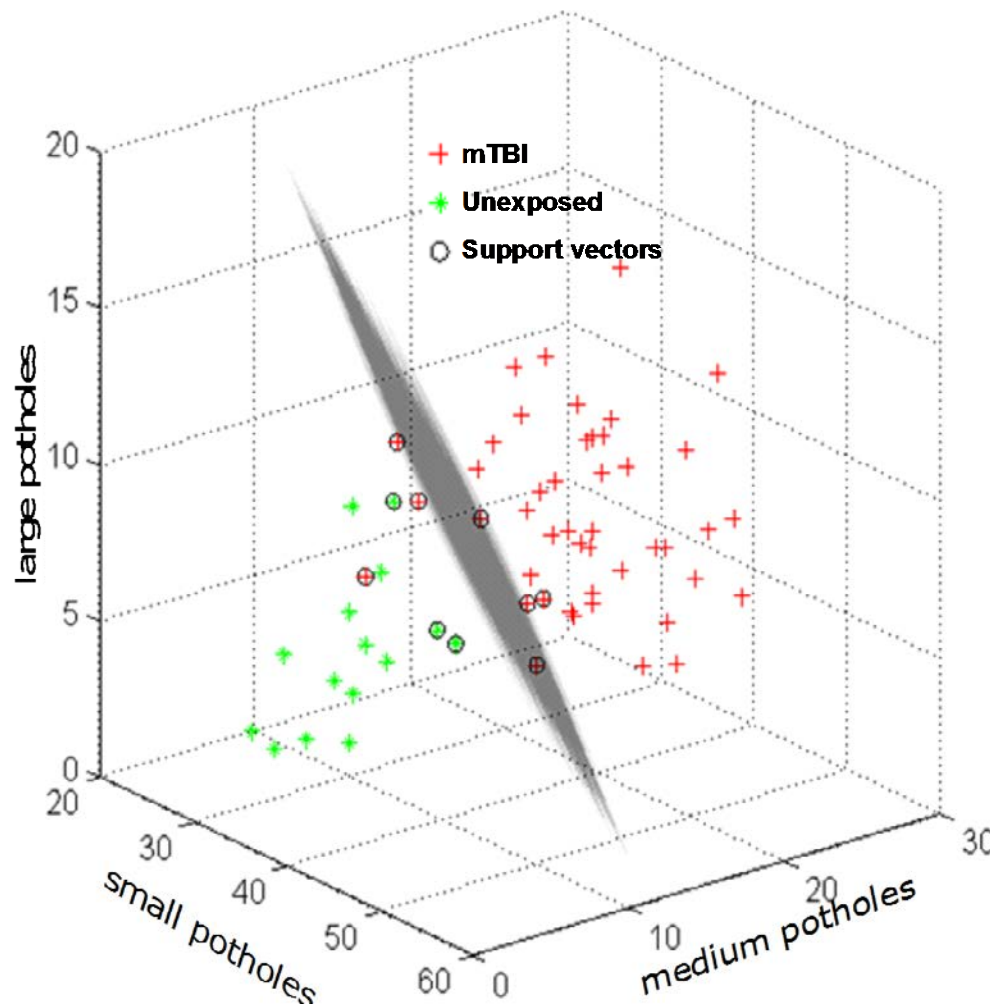
# Optimal separating hyperplane



# Non-linear SVM solution

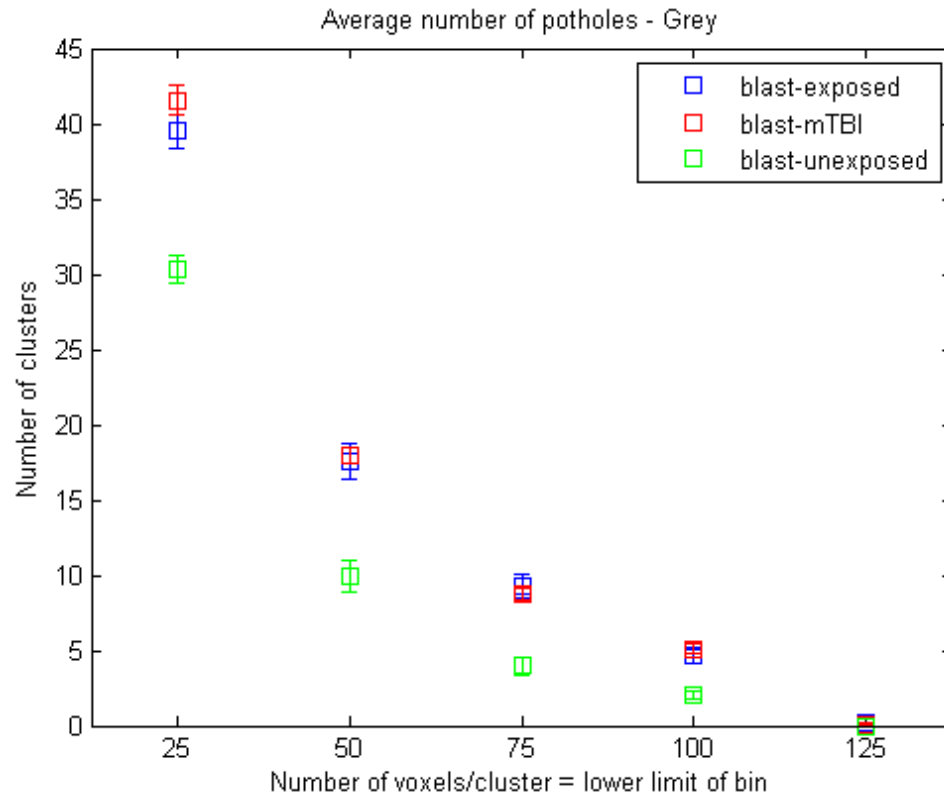


Machine learning (pattern classifier) can help diagnose mild TBI and subconcussive blast exposure



### After Computer Training:

- 98% correct in diagnosing mild TBI
- 96% of subconcussive blast cases were “diagnosed” with mild TBI



**Figure 5.** There was a significant main effect of group [ $F(2,77)=33.8$ ,  $p<.0001$ ] on the number of small (25-50 voxel), medium (50-75 voxel), and large (75-100 voxel) potholes, which were defined by low grey matter volume ( $z < -2$ ). The blast-unexposed control group had significantly fewer potholes than the blast-mTBI group ( $p < .0001$ ) and the blast-exposed group ( $p < .0001$ ). Based on the number of potholes, the blast-exposed group resembled the blast-mTBI group when considered in relation to the blast-unexposed control group ( $p > .3$ ).



# Increased Gray Matter Diffusion Anisotropy in Patients with Persistent Post-Concussive Symptoms following Mild Traumatic Brain Injury

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## Abstract

A significant percentage of individuals diagnosed with mild traumatic brain injury (mTBI) experience persistent post-concussive symptoms (PPCS). Little is known about the pathology of these symptoms and there is often no radiological evidence based on conventional clinical imaging. We aimed to utilize methods to evaluate microstructural tissue changes and to determine whether or not a link with PPCS was present. A novel analysis method was developed to identify abnormalities in high-resolution diffusion tensor imaging (DTI) when the location of brain injury is heterogeneous across subjects. A normative atlas with 145 brain regions of interest (ROI) was built from 47 normal controls. Comparing each subject's diffusion measures to the atlas generated subject-specific profiles of injury. Abnormal ROIs were defined by absolute z-score values above a given threshold. The method was applied to 11 PPCS patients following mTBI and 11 matched controls. Z-score information for each individual was summarized with two location-independent measures: "load" (number of abnormal regions) and "severity" (largest absolute z-score). Group differences were then computed using Wilcoxon rank sum tests. Results showed statistically significantly higher load ( $p=0.018$ ) and severity ( $p=0.006$ ) for fractional anisotropy (FA) in patients compared with controls. Subject-specific profiles of injury evinced abnormally high FA regions in gray matter (30 occurrences over 11 patients), and abnormally low FA in white matter (3 occurrences over 11 subjects). Subject-specific profiles provide important information regarding the pathology associated with PPCS. Increased gray matter (GM) anisotropy is a novel *in-vivo* finding, which is consistent with an animal model of brain trauma that associates increased FA in GM with pathologies such as gliosis. In addition, the individualized analysis shows promise for enhancing the clinical care of PPCS patients as it could play a role in the diagnosis of brain injury not revealed using conventional imaging.

**Citation:** Bouix S, Pasternak O, Rath Y, Pelavin PE, Zafonte R, et al. (2013) Increased Gray Matter Diffusion Anisotropy in Patients with Persistent Post-Concussive Symptoms following Mild Traumatic Brain Injury. PLoS ONE 8(6): e66205. doi:10.1371/journal.pone.0066205

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† These authors contributed equally to this work.

# Potential Clinical and Policy Implications

- Blast-exposure may damage brain tissue (white matter) at comparable levels to mild TBI even in the absence of acute clinical symptoms (subconcussive blast).
- The lack of clinical TBI symptoms following blast exposure may lead to the erroneous conclusion that there is little damage to brain tissue and consequently may go unnoticed.
- If subconcussive blast exposure leads to later chronic symptoms, the patient may be misdiagnosed with clinical entities such as PTSD and depression.
- If confirmed, our findings would support a diagnostic approach that includes novel MRI-based findings that "look below the surface for pathology".

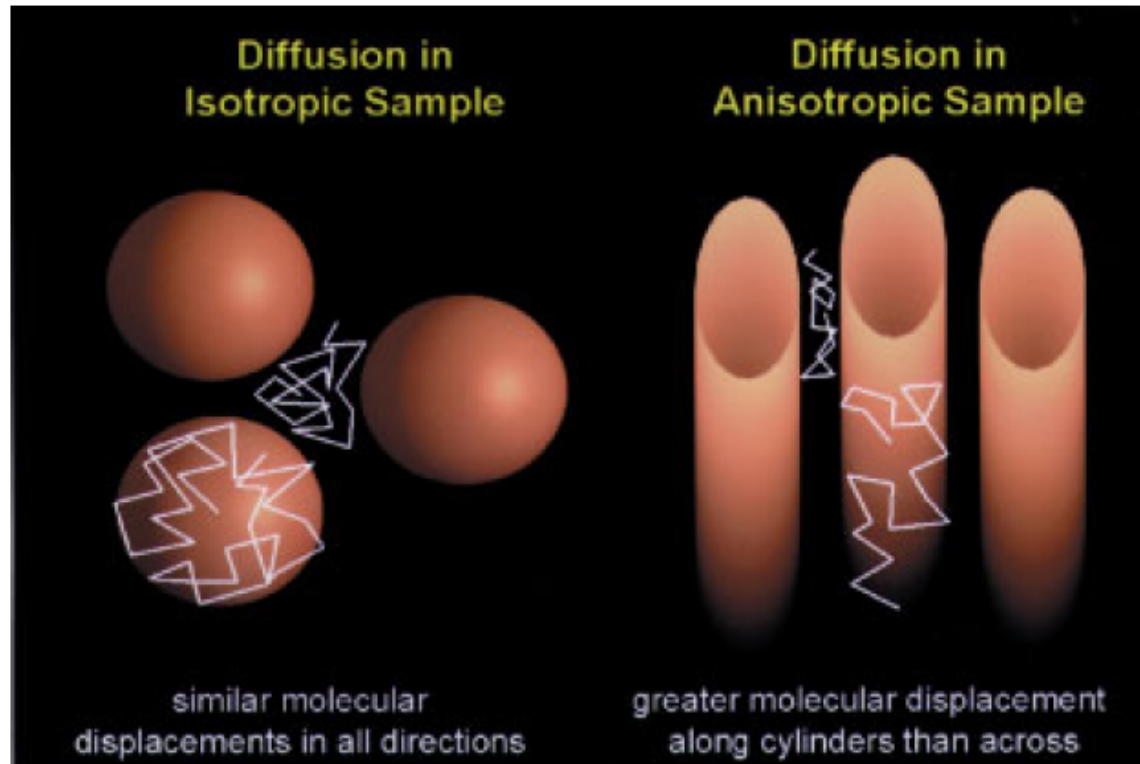
- **Part II**

Quantitative susceptibility mapping (QSM) to achieve myelin-specific imaging in TBI

# Principle of diffusion tensor imaging



# isotropic vs. anisotropic diffusion

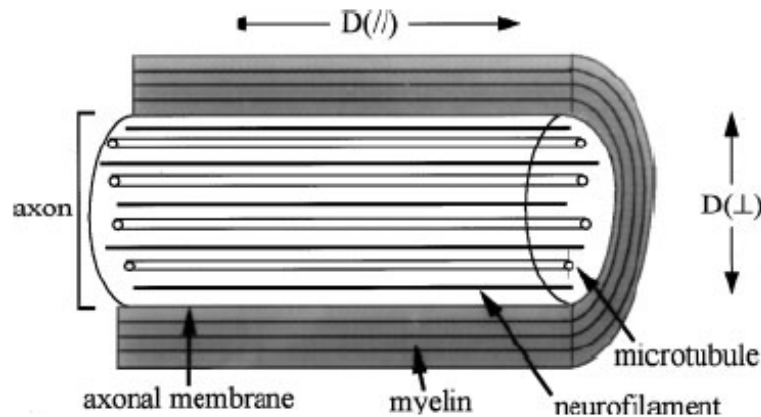


# Quiz Question

What is the principle structure that hinders water diffusion in white matter?



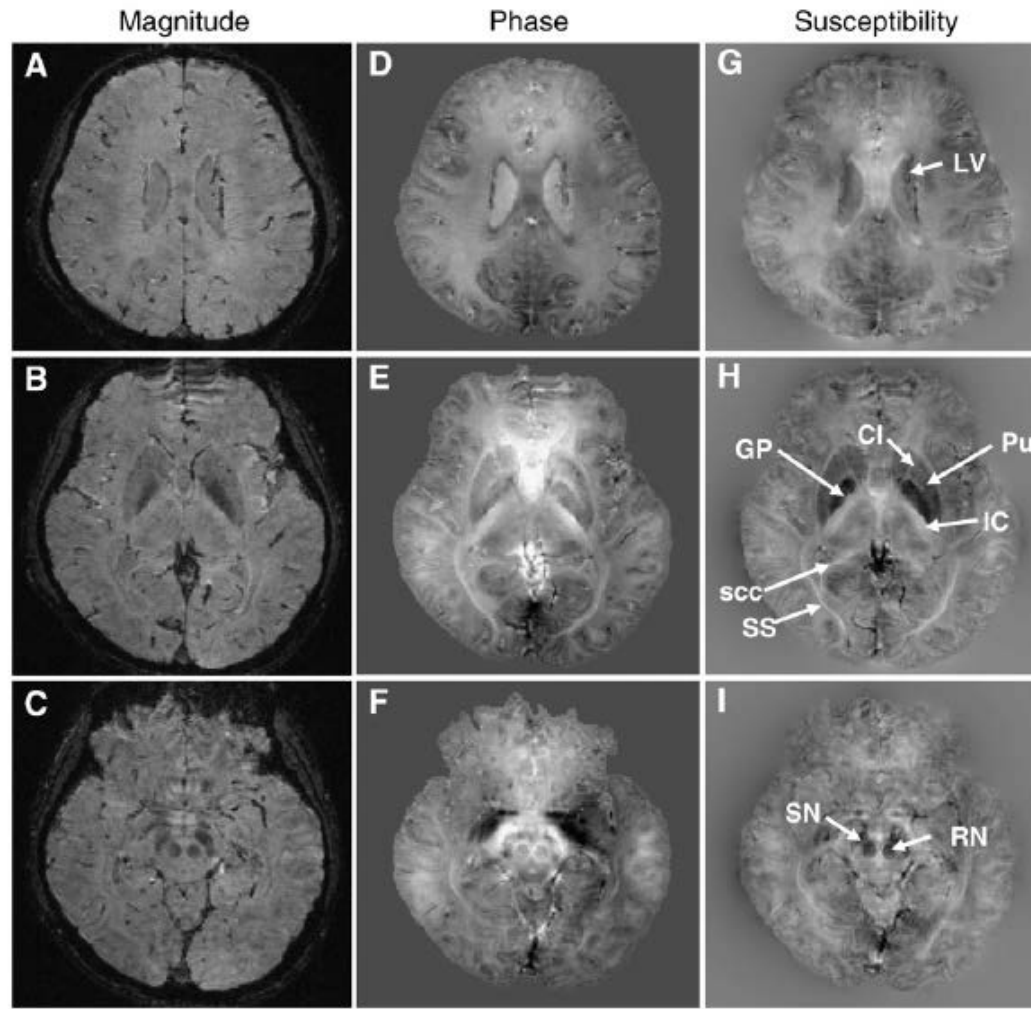
# White matter structure - restricted diffusion



**Figure 4.** A simplistic schematic of the longitudinal view of a myelinated axon. Myelin, the axonal membrane, microtubules, and neurofilaments are all longitudinally oriented structures that could hinder water diffusion perpendicular to the length of the axon and cause the perpendicular diffusion coefficient,  $D(\perp)$  to be smaller than the parallel diffusion coefficient,  $D(\parallel)$ . Other postulated sources of diffusion anisotropy are axonal transport and susceptibility-induced gradients

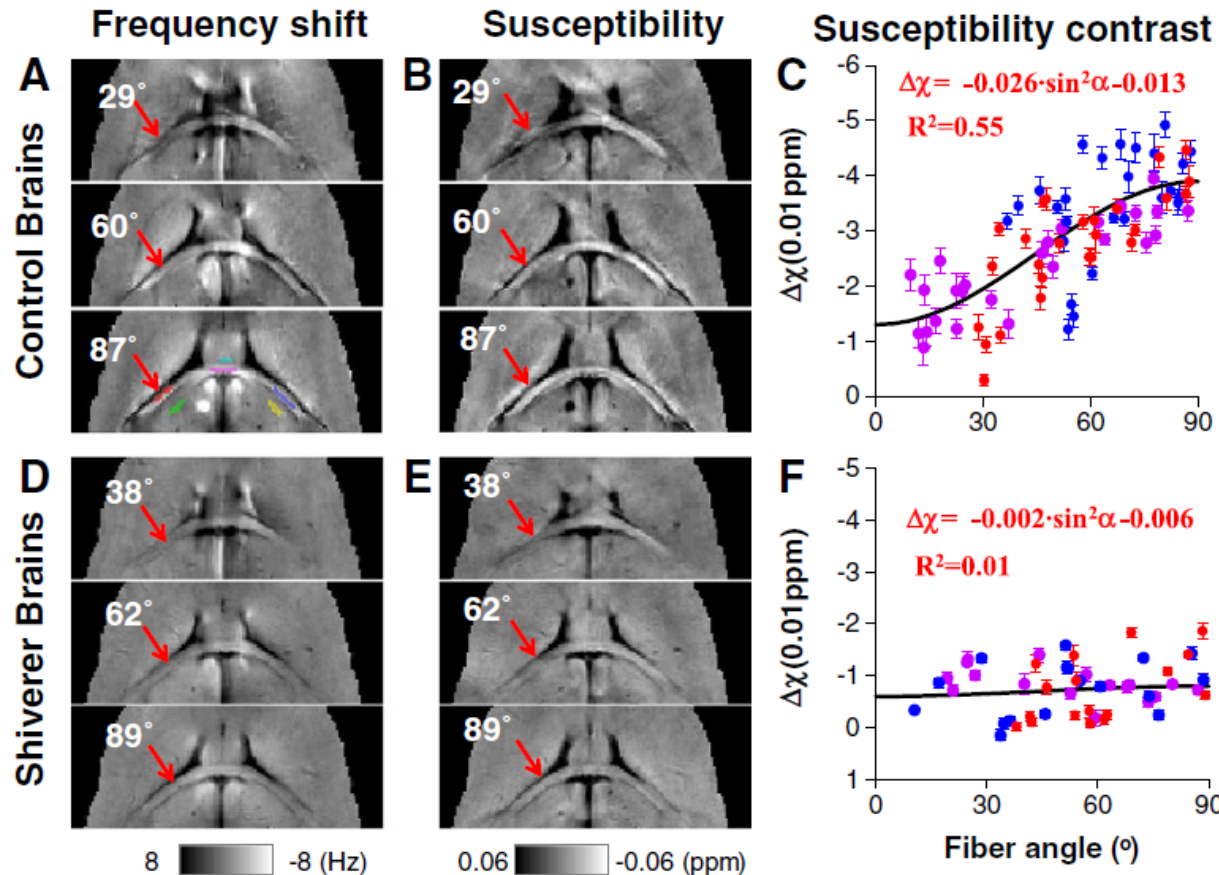
- Water is significantly anisotropic in non-myelinated olfactory nerve of the garfish
- Anisotropy was similar to the trigeminal nerve of garfish myelinated with Schwann Cells
- And similar to the optic nerve of the garfish that is myelinated with oligodendrocytes.

# magnitude, phase, susceptibility images





# How can we image myelin?



- Frequency shift of gradient-echo MRI provides valuable information for assessing brain tissues.
- Frequency and susceptibility contrast depend on white matter fiber orientation
- Source of susceptibility anisotropy in white matter is myelin - loss of susceptibility anisotropy in the dysmyelinating shiverer mouse brain

# Quantitative Susceptibility Mapping (QSM) values

- Iron rich nuclei have positive QSM whereas myelin rich areas have highly negative QSM values.

**Table 1**

Susceptibility of various anatomical structures relative to CSF.

Anatomical structure	Relative $\chi$ (ppm)
CSF (reference)	$0 \pm 0.019$
Red nucleus	$0.032 \pm 0.024$
Substantia nigra	$0.053 \pm 0.026$
Globus pallidus	$0.087 \pm 0.028$
Putamen	$0.043 \pm 0.020$
Caudate nucleus	$0.019 \pm 0.012$
Dentate nucleus	$0.064 \pm 0.034$
Internal capsule	$-0.068 \pm 0.014$
Genu of corpus collosum	$-0.033 \pm 0.013$
Splenium of corpus collosum	$-0.038 \pm 0.013$
Sagittal stratum	$-0.075 \pm 0.019$
Capsula interna	$-0.002 \pm 0.012$

# QSM for investigating TBI

- DTI (FA) is valuable for assessing axon membrane integrity but not myelin integrity.
- While altered FA and Radial diffusivity have been reported in TBI it is unclear if these findings demonstrate myelin damage or damage to other components of white matter.
- QSM provides the ability to isolate the specific components of white matter that are damaged.

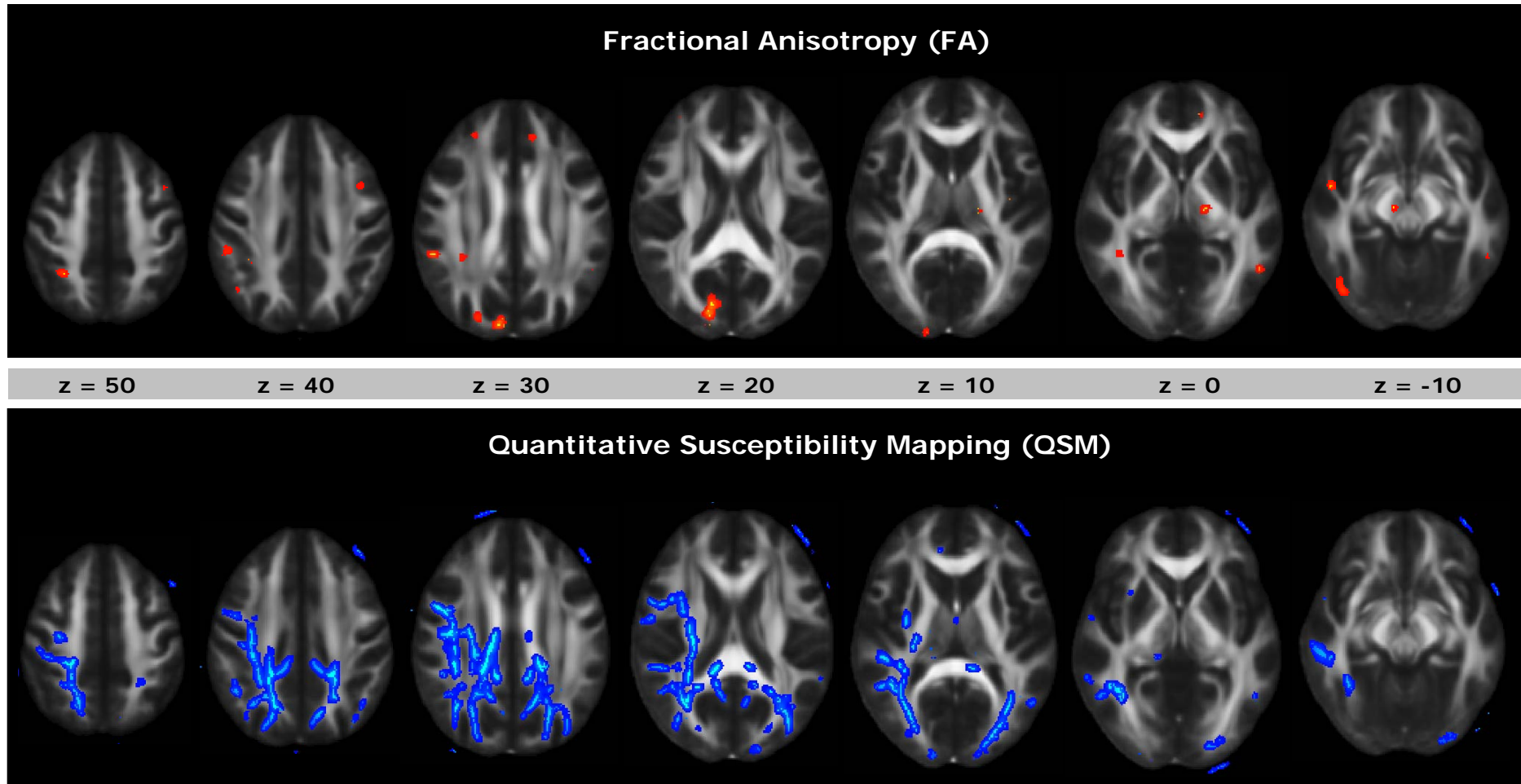
# QSM assessment in Mild TBI

Veterans (n=65) from Iraq and Afghanistan

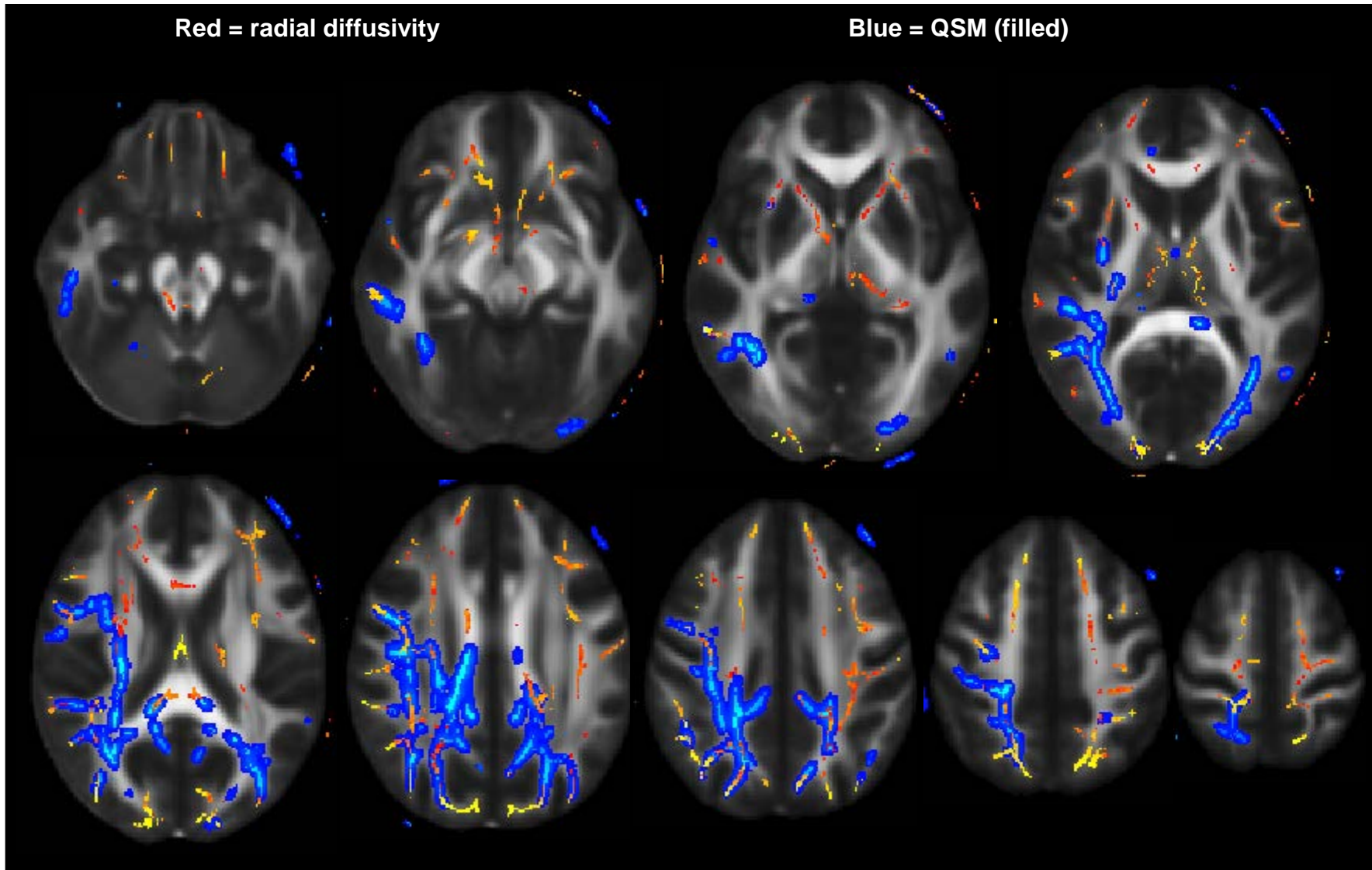
**Table 1. Demographic and Clinical Characteristics of Participants by Group \***

Characteristic	Mild TBI (n=43)	Non-TBI (n=21)	Group Comparison
Age (years), [SD]	40.4 [8.8]	42.0 [9.4]	$t(30) = .67, p > .5$
Gender, No. (%) of females	4 [19]	6 [29]	$\chi^2 (1)=4.0, p = .05$
Handedness, No. (%) right-handed	34 [79]	20 [95]	$\chi^2 (2)=4.1, p > .2$
Race, No. (%) of Caucasian	5 [24]	25[58]	$\chi^2 (3)=8.7, p = .03$
Ethnicity (%) Hispanic	3 (21)	3 (7)	$\chi^2 (2)=3.5, p = .19$
Clinician Administered PTSD Scale [SD]	33.6 (31.9)	13.7 [25.6]	$t(12) = 2.5, p = .016^*$
Loss of Consciousness (any)	16 [37]	0 [0]	$\chi^2 (1)=10.4, p = .001$
Total knocked out [SD]	0.93 (1.87)	0 [0]	$t(12) = 3.3, p = .002^*$

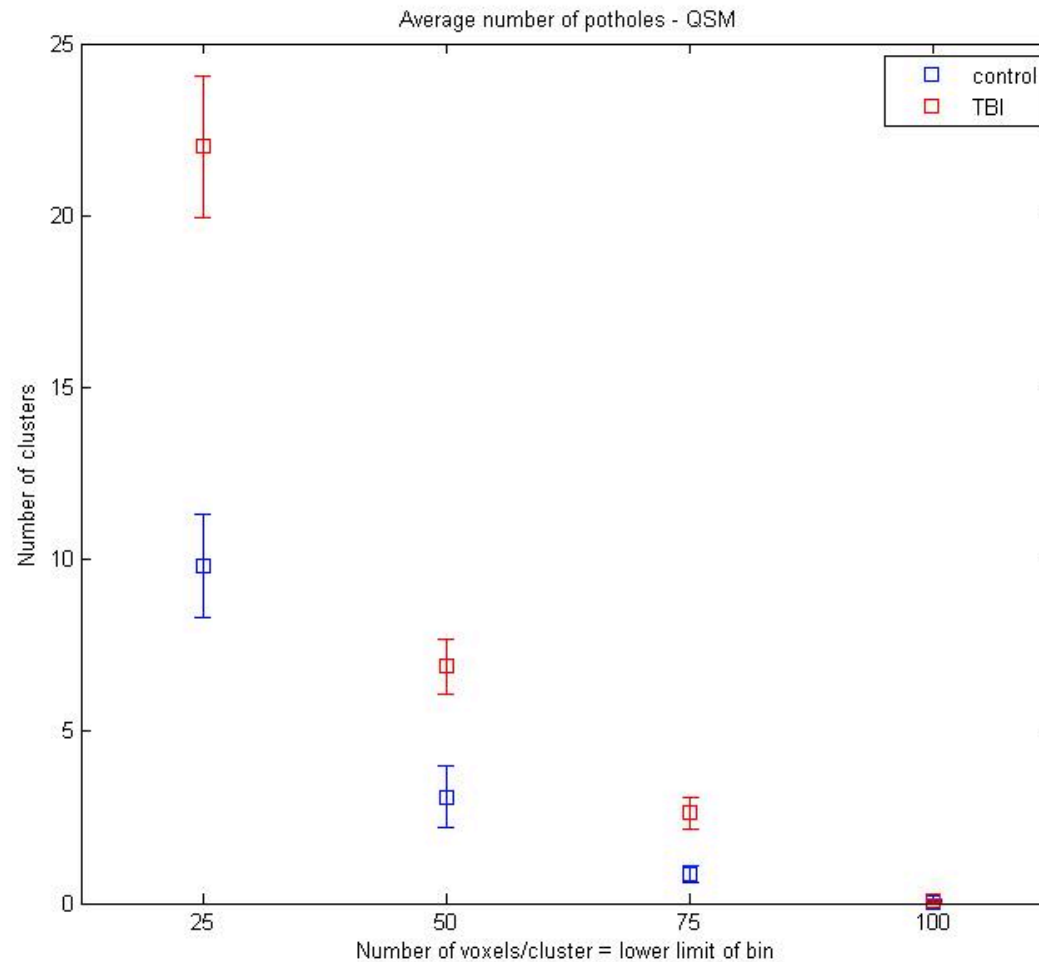
# QSM reveals more TBI associated differences than FA



# QSM vs. Radial Diffusivity



# QSM potholes in mild TBI



# Summary & Conclusions

- FA and radial diffusivity are not ideal for measuring myelin integrity.
- QSM shows dramatically greater differences in mild TBI than FA confirming that damage has occurred to myelin and not just the axon membrane.
- While radial diffusivity has been purported to show myelin diffusivity, further research comparing radial diffusivity to QSM is needed.
- Myelin damage shows interindividual and spatial heterogeneity we saw in FA and radial diffusivity.



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## Lab members and Collaborators

- Shannon Beall
- Vanessa Brown
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- Jasmeet Hayes
- Jeff Hoerle
- Jessica Nasser
- Chris Petty
- Elizabeth Selgrade
- Avani Vora
- Madeline Jacobs
- Gregory McCarthy
- Kevin LaBar
- Chunlei Liu
- Nankuei Chen
- Ryan Wagner
- Ahmad Hariri
- Jonathan Weiner
- Mike Hauser
- Christine Marx

